Parkinsonism and Related Disorders xxx (2017) 1–6

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Does attentional dysfunction and thalamic atrophy predict decline in dementia with Lewy bodies?

Rosie Watson [a], Sean J. Colloby [b, *], Andrew M. Blamire [c], Keith A. Wesnes [d, e, f, g, h], Josh Wood [b], John T. O'Brien [b, i]

[a] The Florey Institute of Neuroscience and Mental Health and The Department of Medicine, Royal Melbourne Hospital, The University of Melbourne, Parkville, Australia
[b] Institute of Neuroscience, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, UK
[c] Newcastle Magnetic Resonance Centre, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, NE4 5PL, UK
[d] Department of Psychology, Northumbria University, Newcastle upon Tyne, UK
[e] Wesnes Cognition Ltd, Streatley on Thames, RG8 9RD, UK
[f] Medical School, University of Exeter, UK
[g] Centre for Human Psychopharmacology, Swinburne University, Melbourne, Australia
[h] Medicinal Plant Research Group, Newcastle University, UK
[i] Department of Psychiatry, University of Cambridge, Cambridge, CB2 0QC, UK

ARTICLE INFO

Article history:
Received 19 June 2017
Received in revised form
27 September 2017
Accepted 8 October 2017

Keywords:
Dementia
Lewy body
MRI
Neuroimaging
thalamus

ABSTRACT

Introduction: To evaluate the clinical characteristics of DLB subjects who died within 1 year of assessment compared to those who survived and investigate their patterns of *in vivo* regional thalamic atrophy using structural MRI.

Methods: Seventy subjects (35 DLB, 35 aged controls) underwent 3 T T1-weighted MR scanning as well as clinical and cognitive assessments, including a computerised assessment of attention. All subjects were contacted after 12 months for reassessment.

For both hemispheres, using FSL FIRST, the thalamus was automatically segmented followed by inter-subject vertex-wise analyses involving group comparisons and behavioural correlates.

Results: There was significant bilateral atrophy in the ventral-dorsal and pulvinar regions in DLB relative to controls ($p_{corrected} < 0.05$). The DLB group was then re-categorised based on 12-month mortality data: DLB-a (n = 26) and DLB-d (n = 9) (a = alive, d = death within 12 months of study assessment). Compared to controls, significant attentional dysfunction and bilateral atrophy of the pulvinar, ventral and dorsal nuclei were observed in DLB-d ($p_{corrected} < 0.05$), whereas in DLB-a, atrophy was far less extensive.

Conclusions: Distinct patterns of thalamic atrophy occur in DLB that may relate to the attentional dysfunction and cognitive fluctuations that characterise this disorder. Relative to controls, the extent of attentional impairment and pattern of thalamic degeneration differ in those patients who died within 12 months of assessment, despite having an otherwise similar level of dementia severity. These findings may provide insight into the neurobiological changes underpinning important clinical characteristics and disease heterogeneity.

1. Introduction

Dementia with Lewy bodies (DLB) is a common form of dementia in late life. It is associated with higher morbidity, mortality and a poorer quality of life when compared to Alzheimer's disease (AD) [1–3]. It is a heterogeneous condition with a proportion of people deteriorating very rapidly until death. However, we do not have a good understanding of the pathophysiological mechanisms underpinning the differing clinical features and the potential influence that they may have on disease course and patient outcomes. A shorter duration of illness has been reported in DLB compared to AD although the reasons were not clear and the difference remained significant even when factors such as age, gender and vascular risk factors were controlled for [1,4].

* Corresponding author.
E-mail address: sean.colloby@ncl.ac.uk (S.J. Colloby).

https://doi.org/10.1016/j.parkreldis.2017.10.006
1353-8020/

Attentional dysfunction is prominent in DLB and related to cognitive fluctuations, one of the core clinical features of the disease [5]. Interestingly, a case series of six patients with DLB and rapid progression had prominent attentional deficits at presentation [6]. The neurobiological correlate of attentional function in DLB is unclear, although increased cognitive fluctuations have been reported to be associated with increased thalamic perfusion in DLB [7].

The thalamus is a key area in maintaining consciousness and is an area vulnerable to Lewy body related pathology [8]. It is an important deep brain structure, key to many sensory, motor and cognitive systems where it has received much interest in the cognitive neurosciences [9] including examination of thalamic structure using magnetic resonance imaging (MRI). Thalamic volume and shape changes have been reported in AD [10–13], while variations in thalamic diffusion and perfusion have been shown in DLB [14–16].

We aimed to evaluate attentional function and patterns of *in vivo* regional atrophy of the thalamus using structural MRI in DLB, comparing the characteristics of DLB subjects who died within 1 year of assessment to those who survived. We hypothesised that those DLB subjects who died within a year would have greater attentional impairment (but not global cognitive impairment) at baseline as well as greater thalamic atrophy than those who survived. As an exploratory analysis, the correlation between attentional function and thalamic shape change was also examined, hypothesising that greater attentional impairment would relate to atrophy in the posterior region (pulvinar) of the thalamus.

2. Methods

2.1. Subjects, assessments and diagnosis

Thirty five individuals over the age of 60 with probable DLB [5,17] were recruited from a community dwelling population of patients referred to local Old Age Psychiatry, Geriatric Medicine or Neurology Services. Thirty-five similar aged healthy control subjects were also recruited from relatives and friends of subjects with dementia or volunteered via advertisements in local community newsletters. The research was approved by the local ethics committee. All subjects or, where appropriate, their nearest relative, provided written informed consent. All subjects underwent clinical and neuropsychological evaluations and the clinical diagnosis of probable DLB was assigned by independent clinical raters as previously described [18]. This included assessment for Rapid Eye Movement (REM) sleep behaviour disorder using the International Classification of Sleep Disorders-II diagnostic criteria B [19]. Assessments included the Cambridge Cognitive Examination (CAMCOG) incorporating the Mini-Mental State Examination (MMSE) [20], the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) [21], Bristol ADL and Neuropsychiatric inventory. Attention was assessed with the Cognitive Drug Research (CDR) computerised assessment system and included measures of Simple Reaction Time (SRT), Choice Reaction Time (CRT) and Digit Vigilance (DigVig) [22].

2.2. MRI data acquisition

Subjects underwent T1 weighted MR scanning on a 3 T MRI system using an 8 channel head coil (Intera Achieva scanner, Philips Medical Systems, Eindhoven, Netherlands) within 2 months of the study assessment, as previously described [18]. The sequence was a standard T1 weighted volumetric sequence covering the whole brain (3D MPRAGE, sagittal acquisition, 1 mm isotropic resolution and matrix size of 240 (anterior-posterior) x 240 (superior-inferior) x 180 (right-left); repetition time (TR) = 9.6 ms; echo time (TE) = 4.6 ms; flip angle = 8°; SENSE factor = 2). The acquired volume was angulated such that the axial slice orientation was standardised to align with the AC-PC line.

2.3. Thalamic segmentation using FIRST

Estimates of thalamic volumes were conducted using the FSL (FMRIB Software Library, ver. 5.06, http://www.fmrib.ox.ac.uk/fsl) tool FIRST. The method used shape and intensity models of the thalamus, constructed from manually segmented T1 datasets (n = 336), generating surface meshes constrained to preserve vertex number and correspondence. Using these learned models, FIRST then searches through linear combinations of shape variations to obtain the most probable surface/shape given the observed set of voxel intensities for the thalamus for each and every subject. Surfaces were then aligned to MNI125 space to enable intersubject vertex-wise analyses [23].

2.4. Statistical analysis

For demographic and clinical data, the Statistical Package for Social Sciences software (SPSS ver. 19.0.0.1, http://www-01.ibm.com/software/analytics/spss/) was used for statistical evaluation. Continuous variables were examined for normality using the Shapiro-Wilk test and visual inspection of variable histograms and assessed where appropriate using parametric (t-tests) and non-parametric (Mann-Whitney U) tests. For categorical data, χ^2 tests were applied. A p-value of $\leq$0.05 was considered significant.

Vertex shape analysis was performed using the FSL script *first_utils* in order to assess group effects and behavioural correlates on a per-vertex basis. Regional changes in the vertices between groups were conducted using a two-sample unpaired *t*-test with age and total intracranial volume (TIV) as confounding variables. Exploratory multiple regression analysis was used to investigate the relationship between regional changes and behaviour in DLB with age as confounding covariate. Statistical inference was evaluated using the program *randomise* with 5000 permutations generating the appropriate statistic images. Results were family-wise error corrected ($p \leq 0.05$) using the threshold free cluster enhancement (TFCE) method [24].

Table 1
Demographic and group characteristics.

	Controls	DLB	Statistic, p value
n	35	35	
Gender (m: f)	20: 15	27: 8	$\chi^2 = 3.2$, 0.08
Age (yrs)	76.7 ± 5.2	78.4 ± 6.9	$t_{68} = 1.1$, 0.3
MMSE	29.1 ± 1.0	20.3 ± 5.3	**$t_{68} = 9.7$, < 0.001**
CAMCOG	97.3 ± 3.8	67.7 ± 15.3	**$t_{68} = 11.2$, < 0.001**
NPI total	Na	21.5 ± 17.1	
UPDRS III	2.0 ± 1.9	26.0 ± 10.7	**$U_{70} = 1225.0$, < 0.001**
SRT_{mean}	319.5 ± 71.5	692.3 ± 592.1	**$t_{68} = 7.0$, < 0.001**[a]
SRT_{SD}	64.4 ± 24.2	308.8 ± 569.3	**$t_{68} = 4.8$, < 0.001**[a]
CRT_{mean}	516.7 ± 92.4	1104.5 ± 737.9	**$t_{68} = 8.8$, < 0.001**[a]
CRT_{SD}	98.8 ± 29.4	477.1 ± 665.3	**$t_{68} = 7.9$, < 0.001**[a]
$Digit\_Vig_{mean}$	424.3 ± 50.5	608.3 ± 109.9	**$t_{68} = 9.3$, < 0.001**[a]
$Digit\_Vig_{SD}$	62.0 ± 20.4	133.3 ± 47.5	**$t_{68} = 8.6$, < 0.001**[a]
ChI use (y: n)	Na	30: 5	

Values expressed as Mean ± 1 SD.
MMSE = Mini mental state examination, CAMCOG = Cambridge cognitive examination, NPI = Neuropsychiatric inventory, RBD = REM sleep Behaviour disorder, UPDRS III = Unified Parkinson's disease rating scale (section III), SRT = Simple reaction time, CRT = Choice reaction time, Digit_Vig = Digit Vigilance.
Bold text denotes statistical significance.
[a] Performed on transformed data.

Please cite this article in press as: R. Watson, et al., Does attentional dysfunction and thalamic atrophy predict decline in dementia with Lewy bodies?, Parkinsonism and Related Disorders (2017), https://doi.org/10.1016/j.parkreldis.2017.10.006